

Anaphylaxis or anaphylactoid reactions occur in 1:5000 to 1:25,000 general anesthetic administrations. The mortality from anaphylaxis related to anesthesia is estimated to be as high as 6%. The multiple physiologic changes occurring before and during general anesthesia might limit or delay recognition of anaphylaxis. Signs of anaphylaxis include flushing or urticaria, hypotension, difficulty with intubation caused by laryngeal edema or increased ventilatory pressure, or inability to ventilate because of bronchospasm. Serum tryptase quantification during or immediately after a presumed anaphylactic type event might be helpful in confirming clinical suspicion, particularly if a postevent sample demonstrates a decrease to normal value after the event.

The causes of anaphylaxis type reactions related to anesthesia are listed in order of approximate frequency of occurrence.

- Muscle relaxants
- Latex
- Antibiotics, particularly  $\beta$ -lactam antibiotics
- Induction agents or hypnotics
- Opioids
- Colloids, particularly dextran, mannitol, or hydroxyethyl starch
- Blood products
- Others, including protamine, isosulfan blue dye for lymph node dissection, gelatin solution used for hemostasis, chlorhexidine, ethylene oxide, radiocontrast media, streptokinase, methylmethacrylate, chymopapain

Muscle relaxants are responsible for more than 60% of reactions during general anesthesia. Most reactions occur because of direct mast cell activation, but life-threatening reactions are usually caused by specific IgE. The shared tertiary or quaternary ammonium group results in cross-reactions among the muscle relaxants. Succinylcholine might be more likely to cause reactions caused by flexibility of the molecule facilitating the cross-linking of specific IgE on mast cell or basophil membranes. Skin testing to specific dilutions of muscle relaxants has been useful in determining the safest agent after a suspected reaction.

Natural rubber latex sensitivity is the second most common cause of perioperative anaphylaxis in some series. The incidence might be decreasing with time. Anaphylaxis caused by latex is more likely to be delayed or occur later during the procedure compared with that caused by muscle relaxants or induction agents. Multiple prior surgical procedures and spina bifida are risk factor factors. As well, healthcare workers are at greater risk of latex anaphylaxis. A US Food and Drug Administration–approved in vitro test for latex-specific IgE is available, although false-negative results occur. A standardized skin-testing reagent is not available in the United States but is in Canada. Latex precautions are indicated if latex sensitivity is confirmed or highly suspected. All procedures should be done latex-safe with no direct contact with any natural rubber latex debris.

Hypnotic induction agents are the third most likely cause of anesthesia anaphylaxis. Intravenous barbiturates have most commonly been responsible, but the reaction rate is probably less than 1:25,000, with the reported occurrence reflecting the common use of barbiturates. Mixing intravenous barbiturates with neuromuscular blocking agents in the same intravenous line might increase the likelihood of reactions. Skin testing has been reported with thioamyl and thiopental at 0.01 and 0.2 mg/mL, respectively. Propofol is a nonbarbiturate induction agent and is useful if sensitivity to barbiturates is suspected. Specific IgE to propofol occurs, but most propofol reactions are due to direct mast cell activation.

Narcotics used in anesthesia commonly cause flushing and urticaria after intravenous administration. The risk of anaphylactic type reactions, in contrast, is very rare. Reducing the rate of opioid administration usually limits the severity of these reactions.

Antibiotics are frequently administered before, during, or immediately after anesthesia and surgery. The most commonly implicated antibiotics resulting in reactions are  $\beta$ -lactams or vancomycin. IgE-mediated

reactions occur in 0.04% to 0.015% of penicillin-treated subjects, and anaphylaxis occurs in approximately 0.001%. Intravenous administration of penicillin results in the most severe forms of anaphylaxis. Penicillin skin testing is useful to identify specific IgE. The sensitivity of penicillin skin testing is approximately 97% if aqueous penicillin and penicillin major determinant (Pre-pen) are used. The lack of a commercially available minor determinant, sensitivity to which can be associated with severe reactions, is an impediment. Percutaneous, followed by intracutaneous, testing with concentrations of up to 3 mg/mL for aqueous penicillin and  $6 \times 10^{-5}$  molar for major determinant are recommended to exclude penicillin allergy. *In vitro* testing for the major determinant is also available, but its negative predictive value is less well established and is less compared with immediate hypersensitivity testing. Skin testing with penicillin derivatives or cephalosporins is not as well studied. Maximum testing concentrations of 1 to 3 mg/mL have been suggested for these other  $\beta$ -lactams. Carbapenems do not cross-react immunologically with penicillin. Desensitization schedules are available to facilitate use of  $\beta$ -lactam antibiotics, if absolutely necessary. Vancomycin administration, particularly rapid administration, might result in life-threatening anaphylactoid reactions. Evidence for both direct histamine release and direct myocardial depression partially explains this phenomenon. These nonimmunologic reactions to vancomycin can be reduced or eliminated by administration of a dilute solution, dissolved in at least 200 mL, that is slowly infused. Anaphylactic IgE mediated reactions to vancomycin occur but are much less common. Skin testing with a concentration of up to 0.15 mg/mL has been reported, but the reliability of this testing is less certain than with penicillin.

Intravenous protamine used to reverse heparin anti-coagulation might cause anaphylactic or anaphylactoid reactions. The latter reactions are characterized by an increase in pulmonary blood pressure. Proposed causes include both immunologic and nonimmunologic mechanisms. A case-control study showed that prior neutral protamine Hagedorn insulin use (odds ratio, 8.18 [2.08, 32.2]), fish allergy (odds ratio, 24.5 [1.24, 482.3]), and other medication allergy (odds ratio, 2.97 [1.25, 7.07]) are independent risk factors. Estimates are that up to 39% of patients undergoing cardiopulmonary bypass have one or more of these risk factors.

Dextran and hydroxyethyl starch (HES), large-molecular-weight polysaccharides, might be used as a nonblood product and for high oncotic fluid replacement during surgery. These agents are rarely associated with adverse reactions, probably because of complement activation. Estimates of reaction rates are 0.008% to 0.08% for dextran and 0.08% for HES. Confirmation of dextran or HES as the cause of an adverse reaction is limited by the absence of accurate serologic or skin tests. Case reports are also in the literature describing systemic reactions to albumin.

### Summary

The ideal of preventing perianesthetic reactions is elusive because of the rare occurrence of reactions; the multiple pathophysiologic mechanisms, many of which are undefined; and the limited ability to test for risk or sensitization. A careful medical history focusing on prior adverse reactions is most important. Any prior medication reactions nonspecifically increase the possibility of adverse reactions, and multiple previous medication reactions are a greater risk.

Previous anesthetic associated reactions should be evaluated thoroughly with specific testing if indicated. IgA-deficient subjects should receive washed red blood cells and no whole blood to avoid exposure to exogenous IgA. Intraoperative antibiotic administration should be at a slow rate with careful hemodynamic monitoring. Drugs with histamine-releasing properties, for example morphine, d-tubocurarine, vancomycin, or quaternary muscle relaxants, should be administered as slowly as possible, particularly in subjects with asthma or cardiopulmonary disease. Risk factors for latex hypersensitivity should be reviewed and consideration given to testing for specific IgE if any risk factors are identified. Pretreatment regimens, as used for radiocontrast anaphylactoid reactions, have not been proved to prevent perianesthetic reactions but might reduce the severity of such reactions.